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In the course of my review of cholinesterase literature, I have identified a publication [Ehrich, M., Shell, L., Roxum, M. and Jortner, B. (1993) Short-term Clinical and Neuropathologic Effects of Cholinesterase Inhibitors in Rats. *J. Am. Coll. Toxicol., 12, 55-68*] (copy appended) which provides important information on the neurotoxicology of a number of cholinesterase inhibiting compounds, *malathion* included. The findings in this publication contrast with the essentially negative FOB parameter findings in the Guideline acute neurotoxicity study (MRID 43146701) of record on malathion as tested at similar doses. This study should be introduced into the record of literature publications pertaining to the neurotoxicology of malathion.

By way of summary (this is not a review of the study), I shall focus my comments on the malathion assessment within this publication. Malathion was evaluated in an acute neurotoxicity study that employed EPA's most recent neurotoxicity functional observational battery (FOB) screening procedure guidelines. Accordingly, malathion (American Cyanamid, 88%) was administered orally to *male* Long Evans rats at the single dose levels of 0, 600, 1000 and 2000 mg/kg, and monitored for clinical signs, FOB parameters (several end points), brain and spinal cord cholinesterase inhibition and neurohistopathology. The FOB was used to screen for neurotoxic effects at days 7, 14 and 21 post-dosing.

In the case of malathion, among FOB parameters examined, increased *activity* was seen at 21 days for the 600 and 1000 mg/kg doe groups, while the same effect was seen by day 14 in the 2000 mg/kg dose group. Exaggerated *response to touch* was evident in the 600 and 1000 mg/kg groups, but "no reaction" (a below normal response) was observed in the 2000 mg/kg group. Difficulty in *ease of removal from cage* was noted for the 1000 mg/kg group at 21 days and in the 2000 mg/kg group by day 14. Exaggerated *reactivity to handling* was noted in the 1000 mg/kg group at day 21, and by day 14 in the 2000 mg/kg dose group. Abnormal *gate* was observed at 21 days in the case of the 2000 mg/kg dose group.

Cholinergic clinical signs were noted only at 2000 mg/kg, but evidently dissipated early and were not present when the FOBs were done on days 7, 14 and 21. Atropine was administered in this study.

Cholinesterase inhibition in both brain and spinal cord was observed at all dose levels, being most remarkable at 2000 mg/kg. There were no neuropathologic lesions seen in neural tissues examined.

The study report claims in its Discussion that: "However, even after signs of cholinergic poisoning were no longer evident, each of the 7 cholinesterase inhibitors (malathion included) used in the present study caused rats to exhibit alterations in one or more of the parameters of the FOB categorized as indicative of changes in behavior or central nervous system excitability during examination 1 to 3 weeks later."

It should be noted that in the case of malathion, a NOEL was not identified for FOB findings, and that this contrasts with the NOEL/LOEL = 1000/2000 mg/kg (based on increased motor activity) in the malathion Guideline acute neurotoxicity of record. In this latter study, malathion (Cheminova 96.5%) was evaluated at the single oral dosage levels of 0, 500, 1000 and 2000 mg/kg at days 1, 7 and 14 post-dosing. There were no effects on guideline FOB parameters at any dose.

It is my understanding this publication was not included among those literature references under review by the FQPA Safety Factor Committee, nor the HIARC, in determining whether further behavioral effects testing, e.g. developmental neurotoxicity, should be required for malathion. It is my recommendation the reference be included among the other references, for future referral.

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Attachments (1)